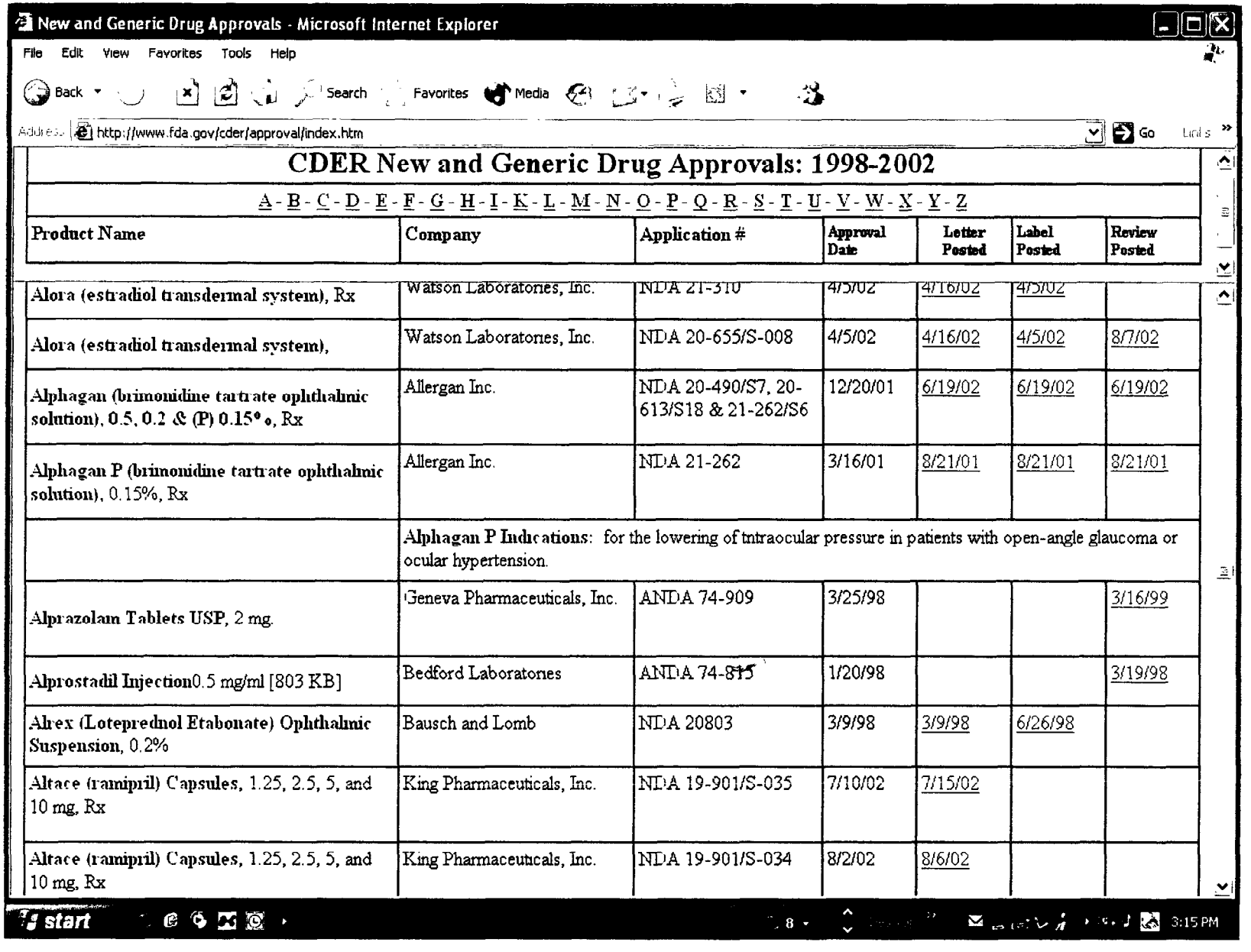
Appendix 1
ALPHAGAN P SBA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Product Name	Company	Application #	Approval Date	Letter Posted	Label Posted	Review Posted
Alora (estradiol transdermal system), Rx	Watson Laboratories, Inc.	NDA 21-310	4/5/02	4/16/02	4/5/02	
Alora (estradiol transdermal system),	Watson Laboratories, Inc.	NDA 20-655/S-008	4/5/02	4/16/02	4/5/02	8/7/02
Alphagan (brimonidine tartrate ophthalmic solution), 0.5, 0.2 & (P) 0.15%, Rx	Allergan Inc.	NDA 20-490/S7, 20-613/S18 & 21-262/S6	12/20/01	6/19/02	6/19/02	6/19/02
Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%, Rx	Allergan Inc.	NDA 21-262	3/16/01	8/21/01	8/21/01	8/21/01
	Alphagan P Indications: for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.					
Alprazolam Tablets USP, 2 mg.	Geneva Pharmaceuticals, Inc.	ANDA 74-909	3/25/98			3/16/99
Alprostadil Injection0.5 mg/ml [803 KB]	Bedford Laboratories	ANDA 74-815	1/20/98			3/19/98
Alrex (Loteprednol Etabonate) Ophthalmic Suspension, 0.2%	Bausch and Lomb	NDA 20803	3/9/98	3/9/98	6/26/98	
Altace (ramipril) Capsules, 1.25, 2.5, 5, and 10 mg, Rx	King Pharmaceuticals, Inc.	NDA 19-901/S-035	7/10/02	7/15/02		
Altace (ramipril) Capsules, 1.25, 2.5, 5, and 10 mg, Rx	King Pharmaceuticals, Inc.	NDA 19-901/S-034	8/2/02	8/6/02		

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APPLICATION NUMBER:

21-262

MEDICAL REVIEW

Endothelial Cell Count

The endothelial cell count analyses was performed on the eye with the most unfavorable change from baseline. Endothelial cell count data were collected at 8 sites in a total of 244 patients. There was no statistically significant difference among treatment groups in endothelial cell count at baseline or the change from baseline at month 3 ($p \geq 0.169$)

Table 27 - Mean Endothelial Cell Count – Study 008

	Brimonidine-Purite 0.15%	Brimonidine-Purite 0.2%	Alphagan
Baseline	2215.3	2317.9	2268
Month 3	2156.4	2308.7	2251.9

Reviewer's Comments: *There were no clinically significant changes in endothelial cell count between baseline and 3 months in any of the treatment groups.*

Cardiovascular

There was no clinically significant changes between or within group differences with respect mean changes from baseline for heart rate and blood pressure at month 3.

Reviewer's Summary of Safety and Efficacy

Brimonidine-Purite 0.15% has an IOP lowering ability which is equivalent to Alphagan.

The average IOP lowering capability of Brimonidine-Purite 0.15% and 0.2% range from approximately

Brimonidine-Purite 0.15%, 0.2% and Alphagan have similar adverse event profiles.

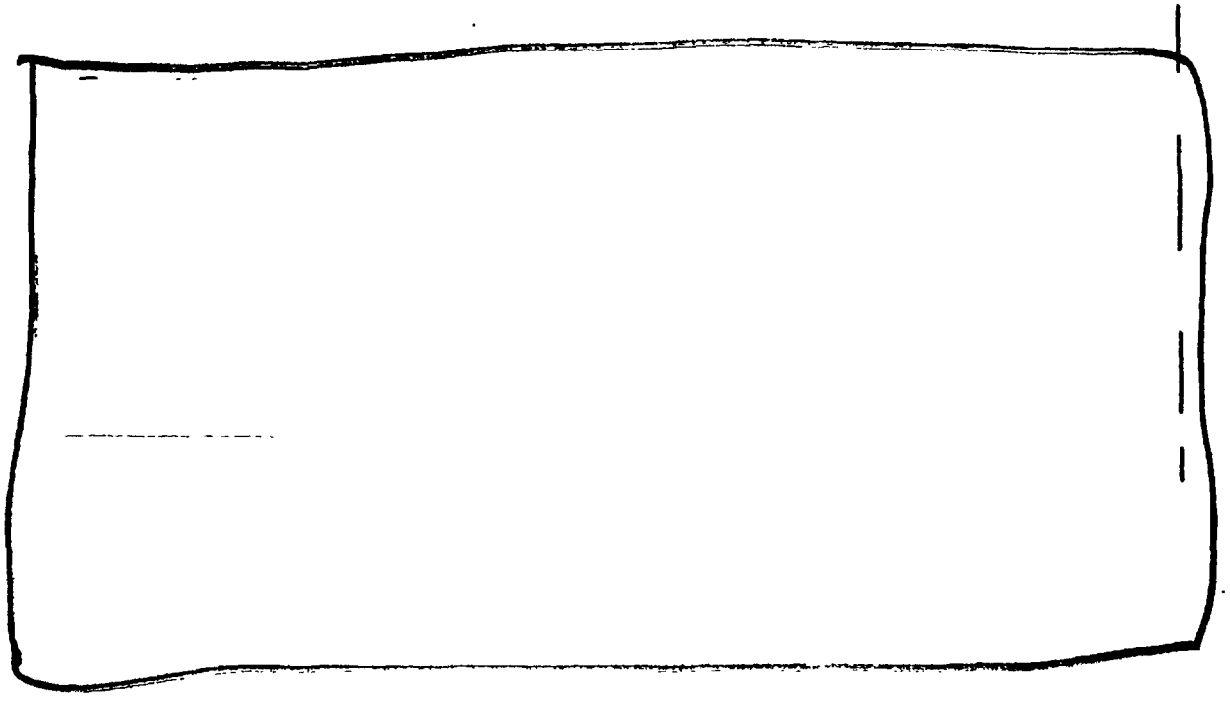
9 Reviewer's Overall Summary of Efficacy and Safety

Brimonidine-Purite 0.15% and 0.2% are equivalent to the currently marketed Alphagan in their ability to lower IOP in patients with ocular hypertension or open angle glaucoma.

Adequate safety has been established for the use of Brimonidine-Purite 0.15% and 0.2% in lowering intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

10 Labeling Review

Reviewer's Comments:
Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.



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APPLICATION NUMBER:

21-262

STATISTICAL REVIEW(S)

2. Discontinuation due to lack of efficacy:

Both Studies 7 and 8 had more patients discontinued treatment due to lack of efficacy in BPOS 0.15% treatment groups compared with that in Alphagan treatment group. Such differences were approaching statistical significant at level 0.05 in the two studies. Combining the two studies, the withdrawal rate due to lack of efficacy was 3.9% in BPOS 0.15% and 1.0% in Alphagan. The p-value for the comparison of BPOS 0.15% to Alphagan was statistically significant at level 0.05 (two sided p-value was 0.011). This analysis suggested that BPOS 0.15% was slightly inferior to Alphagan in lowering IOP.

V. Conclusion:

For BPOS 0.2%, the results of primary analysis on mean IOP change from baseline, the primary end point specified in sponsor's analysis plan, in each individual studies (Studies 7 and 8) consistently satisfied the evaluation criteria of therapeutic equivalence to Alphagan agreed by both the agency and the sponsor.

For BPOS 0.15%, neither study had met the evaluation criteria of therapeutic equivalence to Alphagan based on the analyses of primary end points. The analysis of withdrawal due to lack of efficacy showed that BPOS 0.15% was numerically inferior to Alphagan. However, the results of IOP change from baseline were close to the non-inferiority criteria. The differences of withdrawal rates due to lack of efficacy between BPOS 0.15% and Alphagan were only about 3%. The average change from baseline for BPOS 0.15% treatment group was more than 3 mm Hg for both studies. The integrated analysis of IOP change from baseline by pooling the two studies together marginally satisfied the equivalence criteria. To assess evidence collectively, the two studies showed that the efficacy of BPOS 0.15% was close to that of Alphagan, but somewhat inferior to Alphagan based on the results of the individual studies and criteria agreed upon by the agency and the sponsor.

/S/

Qian Li, Sc.D
Mathematical Statistician

Concur:

/S/

Stan Lin , Ph.D
Team Leader